Carbohydrate Research, 52 (1976) 63–68

SYNTHESIS OF 1,2-*trans*-RELATED 1-THIOGLYCOSIDE ESTERS

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(Received May 1st, 1976; accepted for publication, May 17th, 1976)

ABSTRACT

Boron trifluoride etherate catalyses the condensation of equimolar proportions of 1,2-*trans*-related monosaccharide peresters and thiols to provide a convenient synthesis of esters of 1,2-*trans*-1-thioglycosides. The reaction is efficient with alkyl, alkenyl, and some aryl thiols, and with aldopentose, aldohexose, and hexuronic acid acetates and benzoates. Some limitations are noted.

INTRODUCTION

Current interest in thioglycosides[1] rests in their biochemical action as enzyme inhibitors[2], in their consequent use in affinity chromatography[1a–d,1f,1k,2,3], in other biochemical work[1a], and in their value in glycoside synthesis[4]. Often, acylated glycosyl halides have been used in the synthesis of these substances[5,6], either by treating them with thiolate salts or by converting them by way of isothiouronium intermediates into 1-thiosugars which were then alkylated. In both cases, the generation of the glycosyl–sulphur bond involves a displacement by nucleophilic sulphur at the anomeric centre of the glycosyl halides in processes which, for well-established reasons[7], result in the preponderance of 1,2-*trans*-related products. On occasion, these products have been obtained directly from aldoses, glycosides, and peracetylated sugars by thiolysis reactions under acidic conditions[5,6], but a generally applicable procedure for such thiolyses does not appear to have been proposed.

The Helferich method for preparing aryl glycoside peracetates[8], which involves the fusion of peracylaldoses with phenols in the presence of added acid (usually toluene-*p*-sulphonic acid), was first extended to the preparation of thio-analogues by Hurd and Bonner[9], who prepared phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (but only in 14% yield) by a fusion procedure involving toluene-*p*-sulphonic acid as catalyst. More recently[1c], 1,2,3,4-tetra-*O*-acetyl-L-fucose was treated with *p*-nitrothiophenol, in the presence of the same catalyst and small amounts of acetic anhydride and acetic acid, to give a mixture of products from which each thiopyranoside was isolated in 35% yield after column chromatography. Repetition of this experiment with alteration of the catalyst to zinc chloride, however, gave specifically the β compound, which was isolated in 70% yield. Clearly, therefore, the

catalyst is important in determining the ratio of products obtained, and in this reaction, the protonic acid promoted anomerisation. Other workers have prepared various aryl thioglycosides from aldose peresters by modification of this procedure[1f,1g,10], but excesses of thiols were used and yields of directly obtainable products were not uniformly good.

The first efficient thiolyses of sugar esters were apparently effected by Lemieux and Brice[11], who prepared the acetylated 1,2-*trans*-related ethyl 1-thioglycopyranosides of D-glucose, D-mannose, and D-galactose by use of ethanethiol as solvent and zinc chloride as catalyst. This procedure has associated practical difficulties and cannot readily be applied with non-volatile thiols. The present report describes a similarly homogeneous procedure which uses β-glycosyl esters, equimolar proportions of thiols, chloroform as solvent, and boron trifluoride etherate, which has been used previously to catalyse several carbohydrate reactions but seldom[12] glycosidations.

Other syntheses of thioglycosides involve partial hydrolysis of dithioacetals[5,6,13], thiolysis of Brigl's anhydride[14], pyrolysis of glycosyl xanthate esters[15], additions to unsaturated carbohydrates[16], sulphur extrusions from diglycosyl disulphides[17], and anomerisation of other thioglycosides[18].

DISCUSSION

In keeping with earlier results[11], it was found that, of the anomeric 1,2,3,4,6-penta-*O*-acetyl-D-glucoses, the β isomer reacted the faster when treated in chloroform solution with thiophenol (1.7 mol. equiv.) and boron trifluoride (1.8 mol. equiv.); from both anomers, the β-thioglycoside tetra-acetate was isolated as the main product. The mother liquors contained both glycoside anomers as well as an uncharacterised, less-mobile (t.l.c.) by-product. A general synthetic procedure was then adopted which involved the use of slight molar excesses of thiols, and boron trifluoride concentrations which afforded convenient reaction rates as indicated by t.l.c. analyses. In Table I, the compounds which were synthesised by this method are listed, together with the conditions and efficiencies of their preparations. The procedures are thus applicable to the synthesis of acetylated and benzoylated thioglycosides of pentoses, hexoses, and hexuronic acid derivatives, and alkyl, alkenyl, and aryl thiols can be employed. Allyl thioglycosides were of particular interest because of their potential value in affinity chromatography, and whereas the β-thiogalactopyranoside tetra-acetate was readily obtained, the β-glucoside analogue could not be isolated crystalline despite the use of a seed crystal. N.m.r. and t.l.c. evidence indicated, however, that the reaction proceeded smoothly and that the β-glycoside was the major product in this reaction also.

All of the compounds in Table I, except Nos. **10** and **11**, were prepared from esters having participating groups at C-2. When the reaction was carried out on 2,3,4,6-tetra-*O*-benzyl-α-D-glucose, which has recently been used so successfully in α-glucoside[19] and β-glucoside synthesis[20], smooth conversion occurred to give a mixture of phenyl 1-thioglycosides from which the α and β anomers were isolated,

TABLE I

SYNTHESES OF THIOGLYCOSIDE ESTERS

No.	*Compound*	*Concentration of starting material (% in $CHCl_3$)*	*Thiol (mol. equiv.)*	*BF_3 etherate (mol. equiv.)*	*Time (h)*	*Yield (%) (direct isolation)*	*Characterisation*				
							Found		*Ref.*	*Lit.*	
							M.p. (degrees)	*$[\alpha]_D$ ($CHCl_3$) (degrees)*		*M.p. (degrees)*	*$[\alpha_D]$ ($CHCl_3$) (degrees)*
1	Phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside	20	1.2	5	5	71	117–118	−16	23	117	−17
2	Phenyl tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside	6	1.2	3	1.5 (reflux)	62	167–168 (from acetic acid)	+34	[a]	—	—
3	Phenyl tetra-*O*-acetyl-1-thio-β-D-galactopyranoside	20	1.1	3	43	69	73–76	+5	24	70.5	+5
4	Phenyl tri-*O*-acetyl-1-thio-β-D-xylopyranoside	20	1.1	1.5	1.5	56	79–80	−55	23	78	−59
5	Benzyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside	50	1.3	0.2	46	70	102–103	−92	25	100–101	−91
6	Ethyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside	50	1.1	0.22	35	83	82–84	−26	11	82–83	−28
7	Allyl tetra-*O*-acetyl-1-thio-β-D-galactopyranoside	4	1.05	10	2	58	88–89	+11	26	88–89	+7
8	Methyl (phenyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranosid)-uronate	17	1.2	2.7	18	76	119–120	−20	27	119–120	−22
9	Phenyl 2,5-di-*O*-acetyl-1-thio-β-D-glucofuranosidurono-6,3-lactone	20	1.05	4	2.5	62	115–116 (from ethanol)	−32	[b]	—	—
10	Phenyl tetra-*O*-benzyl-1-thio-α-D-glucopyranoside[d]	3	1.2	5.6	2.5	—	81–82 (from ethanol)	+154	[c]	—	—
11	Phenyl tetra-*O*-benzyl-1-thio-β-D-glucopyranoside[d]	3	1.2	5.6	2.5	—	91–92	+3	4[a]	92–93	+1

[a]Calc. for $C_{40}H_{32}O_9S$: C, 69.8; H, 4.7; S, 4.7. Found: C, 69.8; H, 4.7; S, 4.7. [b]Calc. for $C_{16}H_{16}O_7S$: C, 54.5; H, 4.6; S, 9.1. Found: C, 54.7; H, 4.7; S, 9.1. [c]Calc. for $C_{40}H_{40}O_5S$: C, 75.9; H, 6.4; S, 5.1. Found: C, 76.1; H, 6.5; S, 5.3. [d]Prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-glucose[28] and isolated by preparative t.l.c.

after preparative t.l.c., in 50% and 17% yield, respectively. While this route does not represent a viable synthesis of the latter, which is best obtained from the acetate **1**, it does of the former, because of the difficulty in obtaining phenyl 1-thio-α-D-glucopyranoside[21]. After a seed crystal had been obtained as described above, its use permitted direct isolation of the phenyl tetra-*O*-benzyl-1-thio-α-D-glucopyranoside in 31% yield.

Application of the procedure to 1,3,4,6-tetra-*O*-acetyl-α-D-glucose and thiophenol did not result in a thioglycoside ester with an unsubstituted hydroxyl group at C-2, but gave phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (38% isolated) as the main product. Reaction therefore occurred mainly through a 1,2-acetoxonium ion—as was the case with the β-penta-acetate—rather than by direct displacement of the acetoxyl group from C-1. Such ester migrations are well known in carbohydrate chemistry[22].

The method did not give good access to the desired product when 1,2,3,4,6-penta-*O*-acetyl-β-D-glucose was used with *p*-nitrothiophenol. Although a related synthesis using zinc chloride as catalyst has been reported to give good yields of a *p*-nitrophenyl thioglycoside[1c], the boron trifluoride reaction gave a mixture of products which contained (t.l.c. and n.m.r.) appreciable proportions of the α-penta-acetate and α-thioglucoside tetra-acetate. The reduced nucleophilicity of the thiol apparently permitted anomerisation reactions to compete with the required displacement. Likewise, a mixture of products was obtained when tetra-*O*-acetyl-1-thio-β-D-glucose was used as thiol, the main two having the t.l.c. mobilities of α,β- and β,β-1-thiotrehalose octa-acetate.

EXPERIMENTAL

General synthetic procedures. — The carbohydrate starting-materials were all peracetylated β-glycosyl acetates, except for penta-*O*-benzoyl-β-D-glucopyranose (used for compound **2**) and 2,3,4,6-tetra-*O*-benzyl-α-D-glucose (for compounds **10** and **11**). These compounds and the thiols were dissolved in chloroform, boron trifluoride diethyl etherate was added, and the solutions were left at room temperature except for the reaction with penta-*O*-benzoyl-β-D-glucose which was carried out under reflux. T.l.c. was used to determine when the starting materials had reacted fully, at which times the solutions were washed with saturated, aqueous sodium hydrogen carbonate and then with water. Drying of the chloroform solutions and removal of the solvent gave residues from which the compounds named in Table I (with the exception of **10** and **11**, which were isolated by chromatographic methods) were obtained by direct-crystallisation procedures. The mother liquors contained appreciable proportions of the α products, which consistently were observable as more-mobile compounds than the β isomers on thin-layer chromatograms.

*Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside.* — (*a*) *From 1,2,3,4,6-penta-*O*-acetyl-α- and β-D-glucose.* In initial experiments, the anomeric acetates were separately taken in chloroform (30% solution), thiophenol (1.7 mol. equiv.) and

boron trifluoride etherate (1.8 mol. equiv.) were added, and the solutions were kept in the dark at room temperature. Whereas the β-acetate had undergone complete reaction within 2 days, some of the α anomer was still unreacted after 10 days. After 30 days, the products were isolated as described above and shown by n.m.r. spectroscopy to contain the α- and β-anomeric products in the ratio ~1:4, the major glycoside being isolated in yields of 59% and 71% from the α- and β-acetates, respectively. Chromatographic fractionation of the mother liquors from the preparation involving the β-acetate yielded further β-glycoside (5%) and also phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (8%), m.p. 91–92°, $[\alpha]_D$ +228° (*c* 0.8, chloroform); lit.[21] m.p. 91–92°, $[\alpha]_D$ +234° (chloroform).

(*b*) *From 1,3,4,6-tetra-*O*-acetyl-α-D-glucose.* The tetra-acetate (1 g) in chloroform (10 ml) was treated for 1 h with thiophenol (0.35 g, 1.1 mol. equiv.) and boron trifluoride etherate (2.0 g, 5 mol. equiv.). Two minor products, one having a higher, and the other a lower, chromatographic mobility than the main product, were formed. Normal processing gave the phenyl β-thioglucoside in 38% yield.

*Allyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside.* — The reaction was carried out as usual with penta-*O*-acetyl-β-D-glucopyranose (2.9 g), chloroform (25 ml), 2-propene-1-thiol (1 mol. equiv.), and boron trifluoride diethyl etherate (10 mol. equiv.). Reaction was complete after 1 h, and the products were obtained as a colourless syrup, $[\alpha]_D$ +17.5° (*c* 2, chloroform), which contained (t.l.c. and n.m.r.) mainly the allyl β-thioglycoside ($[\alpha]_D$ −0.5°)[25]. No crystalline material was isolated, despite the use of a seed crystal of the compound which, prepared by the method of Cerny and Pacak[25], was found to be difficult to crystallise.

*Reaction of penta-*O*-acetyl-β-D-glucose with p-nitrothiophenol.* — The peracetate (4.0 g) and *p*-nitrothiophenol (1.7 g, 1.07 mol. equiv.) were treated in chloroform (50 ml) with boron trifluoride etherate (7.3 g, 5 mol. equiv.) at room temperature. Reaction was slow, relative to that conducted with thiophenol, and was not complete in 7 days by which time several products had been formed. Although a product with the chromatographic mobility of the expected β-thioglucoside was present, there were also appreciable proportions of a more-mobile compound (presumably the α anomer), and a less-mobile compound with the mobility of penta-*O*-acetyl-α-D-glucose. Two low-field doublets with couplings of ~4 Hz in the ^{1}H-n.m.r. spectrum of the mixture were consistent with these tentative assignments.

*Reaction of penta-*O*-acetyl-β-D-glucopyranose with 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucose.* — The penta-acetate (2.0 g) and the thiol (1.87 g, 1.0 mol. equiv.) were treated in chloroform (25 ml) with boron trifluoride etherate (3.6 g, 5 mol. equiv.). After 5 days, traces of both starting materials remained, and four less-mobile products had been formed. Of these, the major two had the same t.l.c. characteristics as those of β-D-glucopyranosyl 1-thio-β-D-glucopyranoside octa-acetate and α-D-glucopyranosyl 1-thio-β-D-glucopyranoside octa-acetate. The mixture was not examined further.

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